

FINAL REPORT AND RECOMMENDATIONS
TO THE NEVADA STATE HEALTH DIVISION

**FROM THE EXPERT PANEL* ON CHILDHOOD LEUKEMIA
IN CHURCHILL COUNTY, NEVADA**

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Purpose: This report reviews public health recommendations made by the Expert Panel on Childhood Leukemia on February 15, 2001, highlights the accomplishments of the Nevada State Health Division and its partners, and provides updated recommendations for future activities.

Background:

The Expert Panel on Childhood Leukemia first convened on February 15, 2001 in Reno, Nevada. The panel reviewed NSHD's investigation of childhood leukemia cases (primarily acute lymphoblastic leukemia) that had been recently diagnosed in Churchill County, Nevada. The panel considered possible follow-up actions and identified priorities for NSHD. The panel's first report is available at:

<http://health2k.state.nv.us/healthofficer/Leukemia/FallonExpReport32001.pdf>

At its first meeting, the panel confirmed that the cause of childhood leukemia was unknown. Additionally, no medically accepted methods were available to screen healthy children for leukemia. No single factor was identified as likely to explain the excess number of cases. The expert panel focused on three broad possibilities: 1) an unidentified environmental contaminant, 2) the population mixing theory, and 3) random chance. Panel members emphasized that previous investigations of elevated rates of childhood leukemia had not established a definitive cause. The panel recommended six follow-up steps to NSHD. In addition, the panel also addressed existing elevated arsenic levels in the community water supplies of Churchill County. The panel stated that it was unlikely that excessive arsenic levels in drinking water caused the excess cases of childhood leukemia. The panel recommended that efforts be taken as soon as possible to decrease arsenic exposures, regardless of any relation to childhood leukemia.

Review of Original Recommendations:

Efforts to address the original recommendations have been completed by NSHD and are summarized below.

1. **Efficiently expand case-finding efforts.** The expert panel made this recommendation to ensure that all children who were diagnosed with leukemia while living in Churchill County would be identified.

The children who were diagnosed with leukemia while living in Churchill County came to the attention of NSHD because of concerned citizens and families. This is consistent with how most cancer clusters come to the attention of public health officials. To assess the concern, NSHD had to identify all children who developed leukemia while living in Churchill County. The primary source of this information should have been the Nevada Central Cancer Registry (NCCR). However, in February 2001, the NCCR was not yet been certified by the North American Association of Central Cancer Registries (NAACCR); which is an independent organization that sets quality control standards and guidelines for cancer registries. This lack of accreditation raised concerns about the completeness of the registry and the expert panel recommended that other sources be consulted to identify cases. NCCR has since received a Gold Certification (highest level) from NAACCR and provides accurate information regarding the occurrence of cancer across the state. All children diagnosed with leukemia before the most recent state-wide update of

the NCCR should have been identified by the NCCR. Cases diagnosed since the most recent state-wide update should have immediately come to the attention of the NSHD because of local attention to the problem.

Case-finding by the NSHD was extended to Navy personnel and their families who had ever been stationed at the Naval Air Station (NASF). Navy personnel and their dependants' medical records were reviewed to identify any individual aged 0 through 25, ever stationed at NASF, who had been diagnosed with leukemia. This was done to identify cases among Navy dependents that had resided in Churchill County prior to diagnosis but were living elsewhere when diagnosed. The Navy searched approximately 12 million medical records and identified 50 cases of leukemia; only one case was identified with a previous assignment in Churchill County. This case was already known to the NSHD.

Between 1997 and 2002, 16 children who lived in Churchill County, Nevada at the time of, or prior to, diagnosis are known to have developed leukemia. No child residing in Churchill County has been diagnosed with leukemia since December 2001. Of the 16 children with leukemia, 11 were living in Churchill County at the time of their diagnoses. Among these 11 children, one child moved into the county a few days before diagnosis, three lived there between 12 and 23 months before diagnosis, one lived there between 24 and 35 months, and six lived there more than 36 months. The remaining five children lived outside of Churchill County when diagnosed. The observed/expected case ratio (O/E ratio) for childhood leukemia from 1997 through 2001 was 11 cases observed to one case expected. The five children diagnosed while living outside of Churchill County are not included in this calculation because the number of

children who lived in the county and who moved away is unknown. One child included in these calculations moved to Churchill County just days before diagnosis. Despite inclusion in the O/E ratios, this child's leukemia probably was not related to factors specific to living in Churchill County.

The expert panel believes that since 1997 all children living in Churchill County when diagnosed with leukemia have been identified.

2. **Categorize the observed ALL cases by clinically relevant disease biomarkers.** The expert panel made this recommendation in order to identify differences in the biomarker distributions for the Churchill County case series and other reported case series of childhood leukemia.

Fourteen of 16 case-families consented to have the Centers for Disease Control and Prevention (CDC) contact their child's clinician or treating facility to provide medical records and tissue samples. One family refused to participate in the CDC study and one child was diagnosed after the CDC field study was conducted. Information to differentiate between T-cell and precursor-B cell leukemia was available for 15 case-children (which includes the child of the family who chose not to participate in the study), reflecting the distribution normally seen in case series of childhood leukemia. The hospitals where case-children were diagnosed and began treatment reported that only three children had tests for chromosomal abnormalities. Pretreatment specimens from four case children had been stored for later analyses. It is possible that a relatively small number of case children had been entered into Children's Oncology Group (COG)

protocols that required chromosomal testing or specimen storage. Chromosomal testing or tissue storage appears to have been the exception rather than the rule for this case-series.

The expert panel could not review the distribution of clinical biomarkers for the Churchill County case series because information was not available for 11 of 14 children.

3. **Identify potential excessive environmental exposures unique to the community by testing for current exposures in environmental media or human samples.** The expert panel made this recommendation to identify any existing environmental hazard in the community and, if such hazards were identified, to determine if children with leukemia were more likely to be exposed than other children.

NSHD, CDC, and several collaborating agencies conducted extensive sampling in Churchill County. Biologic and environmental samples were tested for heavy metals, persistent and non-persistent pesticides, polychlorinated biphenyls (PCBs), and volatile organic compounds (VOCs). In addition, the environmental samples were also tested for radon and other radioactive elements. (The final report is available at <http://www.cdc.gov/nceh/clusters/Fallon/default.htm>). Levels of most contaminants measured were not elevated compared with national referent data or existing environmental standards. None of the measured contaminants were associated with the occurrence of childhood leukemia. The community was exposed to elevated levels of a few environmental contaminants; most notable of which were arsenic concentrations in drinking water and people's urine. Thirty-four percent of all participants had urinary arsenic levels above the health-based reference level. This finding indicates that arsenic intake for these individuals were

at, or above, a level considered hazardous. Other noteworthy findings were elevated levels of tungsten in urine and drinking water, chlorpyrifos in urine, and DDE in blood. CDC made specific recommendations to decrease exposures and to further study tungsten. No information is available about health effects from tungsten in drinking water. Follow-up testing in other Nevada towns revealed that tungsten is a naturally occurring element in geologic formations in Nevada and that exposures to tungsten in Churchill County are not unique. The National Toxicology Program has accepted the nomination of tungsten for animal toxicology testing to assess the possible health effects of soluble tungsten compounds.

The expert panel believes that community concerns regarding present-day environmental exposures have been properly assessed. None of the environmental contaminants appears to explain the occurrence of childhood leukemia in Churchill County, Nevada. Arsenic in drinking water will continue to be a health hazard until the water treatment facility becomes operational and people no longer consume arsenic contaminated water from privately owned wells.

4. **Identify potential excessive environmental exposures unique to the community by evaluating contaminant releases into the local environment, and assess the potential for human exposure to such contaminants.** The expert panel made this recommendation to evaluate existing data on past releases of environmental contaminants and to assess the potential for people's exposure to hazardous levels of these contaminants.

The Agency for Toxic Substances and Disease Registry (ATSDR) conducted assessments of existing records in collaboration with the NSHD and other partners. The assessments focused on

the possibility of people being exposed to hazardous levels of contaminants. The agency evaluated information related to surface soils and indoor dust, surface water, sediment, biota, air, and tap water in Churchill County. No exposures of public health concern related to the leukemia investigation were identified. ATSDR also examined the potential for exposures from the NASF, including the JP-8 jet fuel pipeline that supplies the NASF. ATSDR reviewed information about contaminants in groundwater (on and off base), surface water, soil, air emissions from stationary sources, and emissions of jet fuel from jets flying into and out of the NASF. ATSDR concluded that there were no past or present public health hazards from exposures to NASF-related contaminants in the environment. ATSDR documents related to the community and NASF assessments are available at http://www.atsdr.cdc.gov/HAC/PHA/region_9.html#nevada.

The expert panel believes that community concerns regarding past environmental exposures have been properly assessed as a result of reviews of environmental data and evaluations of possibilities for community exposures to this contamination.

5. **Collect and bank biologic specimens for future scientific investigations.** The expert panel made this recommendation to ensure that clinical specimens collected from case children and specimens collected in follow-up studies would be stored and made available to qualified researchers who want to conduct research into the cause of childhood leukemia clusters.

As described above, clinical specimens from four children in the case series were stored. In addition to these specimens, urine, blood, and buccal cells (used to harvest DNA) were collected for analyses in the cross-sectional exposure study conducted by CDC and NSHD. Each study

participant provided up to 21 mL of blood, 32 mL of urine, and two buccal cell swabs. These volumes were sufficient to measure all analytes of interest, including persistent and non-persistent pesticides, PCBs, metals, VOCs, specific infectious agents, and extract DNA. The volumes also allowed for remaining sample to be stored for future testing. All study participants (except one case child sibling who did not provide a sample) have at least one plasma aliquot of approximately 250 uL in storage. Some participants have more than one such aliquot. Fourteen study participants do not have any stored urine aliquots, including two study children who did not provide urine samples. Each stored urine aliquot measures about 2 mL. Buccal cell swabs or purified DNA also are available for most study participants. Specimens collected during the cross-sectional exposure assessment reside in storage at CDC. Clinical specimens for the four case children remain at the location where each child was diagnosed.

The expert panel understands that a limited volume of human blood, urine, and DNA collected during the cross-sectional study remain in storage at CDC and may be available for future research studies.

6. **Determine the time course and characteristics of population movement into the Fallon area for the period 1990 through 2000.** The expert panel requested population data to determine if the community had experienced a dramatic increase in its population before 1999.

Sudden dramatic population increases have been associated with other clusters of childhood leukemia. One current theory explaining this association is the Population Mixing Hypothesis. This hypothesis has been applied to isolated or rural communities assumed to contain a high

percentage of children with limited exposure to some infectious agents and hence limited immunity to these agents. The incoming population is assumed to suddenly introduce into the community one or more of these infectious agents, and the ensuing epidemic that occurs as infection spreads through the non-immune population of children in the community somehow increases the rate of leukemia for these children.

Data on the total population, school enrollment, and Navy base personnel were provided to the panel. This information showed a steady increase in the population during the 1990's from 18,028 to 23,405. Likewise, the school-aged children (K-12) who were dependents of Navy personnel increased from 438 children in 1990 to 531 children in 2000, with a peak in 1995 at 626. No dramatic changes were noted in the overall population or among K-12 Naval dependents in the years preceding the cluster of childhood leukemia cases. The permanent military population at the NASF remained fairly constant from 1990 through 2000, ranging between 920 and 1,229 people. However, since 1992 a large number of personnel have been temporarily assigned to the NASF for training. Between 1993 and 2000, the NASF reported that 20,000 to 50,000 temporary personnel annually trained at the base.

The panel reviewed the population changes and believes that these changes may or may not fit those described by the Population Mixing Hypothesis. Clearly, no significant increase in the number of permanent Fallon residents was observed in the years prior to the cancer cluster. In most instances in which the Population Mixing Hypothesis has been cited, a sudden increase in the permanent population was noted. However, the very large population shifts caused by transient military personnel arriving and departing the base are worth noting. If this transient population has the opportunity to infect members of the resident population with infectious agents

to which the community's children have limited immunity, perhaps the Population Mixing Hypothesis applies to the Churchill County cancer cluster. At the same time, the Churchill County population may not include a high percentage of children with limited immunity to infectious agents because the transient population is exposing the local residents to viral illnesses on a constant basis.

7. **Excessive Arsenic Concentrations in Drinking Water.** The expert panel believed that the high levels of arsenic in the municipal water supply were not likely associated with childhood leukemia in Churchill County, Nevada. Even so, the panel recognized that excessive arsenic levels in the municipal drinking water were well above those levels considered to be safe and recommended that levels be reduced.

At the time of the expert panel meeting, the only treatment of municipal drinking water was disinfection by chlorination. A water treatment plant did not exist and it was determined that the municipal water source had remained the same for at least 60 years. The design and implementation of a treatment system by the city was made dependent upon the U.S. Environmental Protection Agency (EPA) setting a permanent maximum contaminant level standard for arsenic, which was not established until November 1, 2001. In the meantime, Fallon disclosed its water arsenic content and the potential health hazards to each user. In April 2000, Fallon contracted an environmental engineering firm to (a) prepare for arsenic removal, (b) design the treatment facility, and (c) choose a location. Construction of the new treatment plant was substantially completed in December, 2003. City officials report that Fallon will be in

compliance and meeting all federal requirements by the end of April 2004.

Several additional efforts have been made to decrease people's exposure to arsenic in drinking water. The Nevada Cooperative Extension's Guard Our Local Drinking Water (GOLD) Program began an educational campaign to encourage people having private wells to have their water tested for arsenic content. In addition, the GOLD Program assisted homeowners by providing low cost to test drinking water wells and interpret test results. Recently, bottled water has been made available to children attending local schools.

The expert panel understands that several efforts have been made to decrease arsenic exposures to residents of Churchill County. Given that (a) arsenic is naturally occurring in the local ground water, (b) that treatment or replacement of drinking water is expensive, and that (c) individuals using private well water are not covered by the Safe Drinking Water Act (SDWA), the panel expects solutions to this problem to occur incrementally over the next several years.

Conclusions

The cause(s) of childhood leukemia, including those from Churchill County, Nevada, remain unknown. Statistical testing of the time and space clustering of childhood leukemia cases in Churchill County from 1999 through 2001 indicate that the likelihood that the cluster was a "random event" is very small. Even so, random chance cannot be excluded as a possible explanation. Statistical tests cannot be used to determine the likelihood that the cluster was due to an unidentified common cause.

The expert panel has been reassured that no previously unrecognized human health hazards were identified in the community, given the thoroughness of the environmental assessments. The

lack of any association between childhood leukemia and environmental contaminants in Churchill County diminishes the possibility that an environmental contaminant caused the leukemia cluster. Community concerns regarding jet fuel exposures were evaluated and do not appear to pose a community health hazard. Additional health information is needed to interpret the high levels of tungsten found in the urine of people living in Churchill County and in other areas of Nevada where drinking water levels of tungsten may be high. It seems unlikely that tungsten could explain the childhood leukemia cluster because (a) no association between leukemia and tungsten was found in the cross-sectional study, (b) tungsten was likely present in the environment for many years, (c) tungsten exposures do not appear unique to Churchill County, and (d) tungsten is not considered a carcinogen. The remaining human health concern related to the local environment continues to be arsenic in drinking water, even though arsenic does not appear to be related to childhood leukemia.

No child living in Churchill County, Nevada has been diagnosed with leukemia since December 2001. The last child who had previously lived in Churchill County but resided elsewhere when diagnosed with leukemia was diagnosed in July 2002. At some time in the future, another child living in Churchill County may be diagnosed with leukemia. Until the causes of childhood leukemia are better understood, it will not be possible to link new cases with those that have already occurred. The next case will, no doubt, be accompanied by urgent requests for additional investigations. The expert panel is providing recommendations to NSHD and researchers to help them prepare to respond when the next case of childhood leukemia is diagnosed.

RECOMMENDATIONS

I. PUBLIC HEALTH PRACTICE

a. Surveillance for Additional Cases

- i. NSHD should continue to use NCCR to conduct surveillance for childhood leukemia. It is important to adequately support NCCR in order for the state to adequately respond to community concerns about cancer clusters. In addition, NSHD should encourage Churchill County clinicians to directly report newly diagnosed cases of childhood leukemia to the state epidemiologist.
- ii. NSHD should consider collecting information about newly diagnosed cases using their existing data collection instrument and should consider collecting blood and urine samples for storage for future research. The panel does not encourage the reanalyzing of questionnaire data or duplicating the cross-sectional study analyses of biologic samples with each additional new case. This activity would require pre-approval by an appropriate Institutional Review Board (IRB).

b. Environmental Contaminants

- i. In the absence of compelling new information, the expert panel does not recommend additional testing of people or the environment in connection with childhood leukemia. As new information becomes available, the NSHD should use professional judgment to determine what further actions are required.
- ii. Given that the treatment of the Fallon municipal water supply should reduce arsenic exposures for those whose drinking water comes from this source, efforts should be made to continue to identify other arsenic contaminated water supplies

in the community and to decrease hazardous exposures.

c. Stored Tissues

NSHD and CDC should determine if existing samples can be made available for future research. Location of the samples should be negotiated.

II. FUTURE RESEARCH

- a. In the absence of compelling new information, the expert panel does not recommend specific follow-up research of the Churchill County cluster at this time. Appropriate IRB approvals should be identified within these guidelines.
- b. NSHD and CDC should consider establishing guidelines permitting access to qualified researchers to use the tissue bank of previously collected materials.
- c. A Research Review Panel (RRP) comprised of nationally recognized experts in childhood leukemia research should replace the existing Expert Panel. The purpose of the expert panel was to review and recommend public health practice activities for the NSHD. The purpose of the RRP would be to review research proposals developed to study the Churchill County leukemia cluster by using existing data or collected specimens. The RRP should include, but not be limited to, scientists from the NSHD and its partners.
- d. The expert panel recognizes the need to identify preventable causes of childhood leukemia and encourages continued etiologic research of childhood leukemia by federal agencies and COG. To succeed, scientists should establish testable theories about the causes of childhood leukemia, develop the technologies necessary to test these theories, and find the opportunities to conduct these tests.

- e. COG has developed a protocol for collecting and banking clinical specimens from all children diagnosed with ALL. Such a tissue bank would ensure that clinical specimens are available for follow-up investigations.
- f. To date, investigations of childhood leukemia clusters have been disappointing for researchers, health departments, and communities. Additional efforts to establish and study biologically plausible theories and testable hypotheses for childhood leukemia clusters are warranted.